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**SARS-CoV-2 infection of primary human lung epithelium for COVID-19 modeling and drug discovery.**

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**Public Summary:**

Coronavirus disease 2019 (COVID-19) is the latest respiratory pandemic caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2). Although infection initiates in the proximal airways, severe and sometimes fatal symptoms of the disease are caused by infection of the alveolar type 2 (AT2) cells of the distal lung and associated inflammation. In this study, we develop primary human lung epithelial infection models to understand initial responses of proximal and distal lung epithelium to SARS-CoV-2 infection. Differentiated air-liquid interface (ALI) cultures of proximal airway epithelium and alveosphere cultures of distal lung AT2 cells are readily infected by SARS-CoV-2, leading to an epithelial cell-autonomous proinflammatory response with increased expression of interferon signaling genes. Studies to validate the efficacy of selected candidate COVID-19 drugs confirm that remdesivir strongly suppresses viral infection/replication. We provide a relevant platform for study of COVID-19 pathobiology and for rapid drug screening against SARS-CoV-2 and emergent respiratory pathogens.

**Scientific Abstract:**

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